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(54) Title: SUSTAINED RELEASE PROPRANOLOL TABLET

(57) Abstract

A method of providing a patient suffering from cardiac arrhythmia with a sustained dosage of propranolol over a prolonged period of time comprises orally administering to the patient a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over a prolonged period of time which is contained in compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for the compressed granules.

SUSTAINED RELEASE PROPRANOLOL TABLET

Background of the Invention

The present invention relates to a sustained release preparation of propranolol. Specifically, it relates to an oral dosage form which provides a release period suitable for single daily dosing while exhibiting good bioavailability.

Propranolol is a well known and widely use beta-adrenergic receptor blocking agent. In the oral formulations currently in use, propranolol is almost completely absorbed from the gastrointestinal tract, but it is subject to rapid liver metabolism. Administration with food has been reported to enhance its bioavailability. The biological half-life ranges from 3 to 6 hours after oral administration. This relatively short half-life is due to the "first pass" effect.

Propranolol is effective in the treatment of hypertension, cardiac arrhythmia and angina pectoris and is indicated in the prophylaxis of common migraine headaches. It is desirable to maintain a constant plasma propranolol level to compete with available beta receptor sites thereby blocking the chronotropic and inotropic responses to catecholamines. Therapeutic doses of propranolol decreases heart rate, cardiac output and blood pressure.

Summary of the Invention

A method of providing a sustained release of propranolol over a prolonged period is provided for patients suffering from hypertension, cardiac arrhythmia, and angina pectoris, and for common migrane headache prophylaxis, which comprises administering to the patient an oral sustained release dosage form. This oral sustained release dosage form is a tablet containing sufficient propranolol to provide a sustained release over a prolonged period contained in granules formed into said tablet, said tablet consisting essentially of a plurality of compressed granules consisting essentially of from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said granules.

The oral sustained release dosage unit form comprises an important aspect of the present invention, permitting a sustained release of propranolol over a prolonged period of time.

Detailed Description of the Invention

Included in the tablet is hydroxypropyl methylcellulose in an amount of about 20 to about 200 mg, with 50 mg being preferred. The hydroxypropyl methylcellulose has the molecular weight of about 20,000 to about 140,000, preferably about 140,000.

Also included is hydroxypropyl cellulose, present in an amount of about 20 to about 200 mg, preferably about 100 mg. The hydroxypropyl cellulose has a molecular weight in the range of from about 60,000 to about 300,000 with 60,000 being a particularly preferred embodiment.

The tablet also includes a lubricant such as magnesium stearate to aid in the tableting process. The

magnesium stearate may be replaced wih other suitable tablet lubricants.

The tablet to the present invention may vary widely in the amount of propranolol that is included. The therapeutic range of 40 to 480 mg per tablet is indicated to control blood pressure, angina, arrythmia and migraine, with 80 and 160 mg tablets being preferred. The oral dosage form herein described provides a release period suitable for once a day dosing.

The following non-limiting examples serve to further illustrate the invention:

EXAMPLE I

The following components are blended and granulated with an isopropyl alcohol-water (4:1) mixture:

propranolol HCl	160 gm
hydroxypropyl methylcellulose (Methocel K4M, Dow)	50 gm (m.w. 86,000)
hydroxypropyl cellulose (Klucel LF, Hercules)	100 gm (m.w. 100,000)

The resulting granules are then dried at 50°C and ground through a 14 mesh screen. The granulated mixture is lubricated with 3 gm (approximately 1%) magnesium stearate. The resultant granules are then compressed into capsule-shaped tablets, each weighing 313 mg.

According to U.S.P II dissolution test methods, i.e., one hour in simulated gastric fluid followed by simulated intestinal fluid, the following data was collected:

Time (in hours)	Percent Propranolol Released
1	20.4
2	32.1
4	48.6
6	64.1
8	80.3
10	87.6
12	94.7

EXAMPLE II

To determine the effectiveness of the oral sustained release dosage form of the present invention, a 24 hour single dose study was made with a standard, commercial propranolol sustained release formulation (Inderal LA; Ayerest, marketed in Canada) which was used for comparison. Both sustained release formulations contained 160 mg propranolol. In addition, a four times daily dosage was administered with a standard non-sustained release Inderal formulation ("Reference", 40 mg Q.I.D.). The results were analyzed by plotting concentration of propranolol against time. The results of area under the concentration-time (AUC) curve are as follows:

	AUC (mg/hr/ml)		
Experiment	The Invention	Inderal LA	Reference
A	1445	313	1041
B	1413	786	7026
C	900	239	1778
D	559	114	658
Mean	1079	363	2625

With respect to the comparison of the sustained release tablet of the present invention ("The Invention") versus the sustained release formulation of the prior art ("Inderal LA"), it is seen that the present invention provides a better bioavailability. The data for Experiment B, "Reference", appears skewed.

WHAT IS CLAIMED IS:

1. A method of providing a patient suffering from cardiac arrhythmia with a sustained dosage of propranolol over a prolonged period of time which comprises orally administering to said patient a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over said prolonged period of time which is contained in compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said compressed granules.

2. The method of claim 1, wherein a substantially constant plasma level of propranolol is maintained over said prolonged period.

3. A method of claim 1, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

4. A method of claim 1, wherein said hydroxypropyl cellulose has a molecular weight of from about 60,000 to about 300,000.

5. A method of claim 1, wherein the weight ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose is about 2:1.

6. A method of providing a patient suffering from angina pectoris with a sustained dosage of propranolol over a prolonged period of time which comprises orally administering to said patient a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over said prolonged period of time which is contained in compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said compressed granules.

7. The method of claim 6, wherein a substantially constant plasma level of propranolol is maintained over said prolonged period.

8. A method of claim 6, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

9. A method of claim 6, wherein said hydroxypropyl cellulose has a molecular weight of from about 60,000 to about 300,000.

10. A method of claim 6, wherein the weight ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose is about 2:1.

11. A method of providing a patient suffering from hypertension with a sustained dosage of propranolol over a prolonged period of time which comprises orally administering to said patient a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over said prolonged period of time which is contained in compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said compressed granules.

12. The method of claim 11, wherein a substantially constant plasma level of propranolol is maintained over said prolonged period.

13. A method of claim 11, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

14. A method of claim 11, wherein said hydroxypropyl cellulose has a molecular weight of from about 60,000 to about 300,000.

15. A method of claim 11, wherein the weight ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose is about 2:1.

16. A method of protecting a patient susceptible to migrane from the appearance of the headache symptoms of said migraine, which comprises the prophylactic oral administration of a tablet consisting essentially of a therapeutically effective amount of propranolol to provide a sustained release thereof over said prolonged period of time which is contained in compressed granules having from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said compressed granules.

17. The method of claim 16, wherein a substantially constant plasma level of propranolol is maintained over said prolonged period.

18. A method of claim 16, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

19. A method of claim 16, wherein said hydroxypropyl cellulose has a molecular weight of from about 60,000 to about 300,000.

20. A method of claim 16, wherein the weight ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose is about 2:1.

21. An oral sustained release dosage unit form which comprises a tablet containing sufficient propranolol to provide a sustained release over a prolonged period contained in granules formed into said tablet, said tablet consisting essentially of a plurality of compressed granules consisting essentially of from about 0.1 to about 10 parts by weight hydroxypropyl methylcellulose and about one part by weight hydroxypropyl cellulose and a lubricant for said granules.

22. The method of claim 21, wherein a substantially constant plasma level of propranolol is maintained over said prolonged period.

23. A method of claim 21, wherein said hydroxypropyl methylcellulose has a molecular weight of from about 20,000 to about 140,000.

24. A method of claim 21, wherein said hydroxypropyl cellulose has a molecular weight of from about 60,000 to about 300,000.

25. A method of claim 21, wherein the weight ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose is about 2:1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/00968

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3] A61K 9/24 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched [4]	
Classification System	Classification Symbols
US	424/21,330

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

Chemical Abstracts, Volume 97 - 2-Propanol-1-[(Cl-Methylethyl) amino)] -3--(1-Naphthalenyloxyl/Cellulose ethers, 2-hydroxyprohy and 2-hydroxypropyl, methyl ester

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category [6]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,248,856, published 03 February 1981 Guley et al.	1-25
X	N, Chemical Abstracts, Vol. 94 (1981), 52973e, Yissum and Vol. 94 (1981), 52962a Teijin Ltd.	1-25

[6] Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [1]	Date of Mailing of this International Search Report [2]
19 August 1983	26 AUG 1983
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Stanley J. Friedman